Remarks/Arguments

A. Pending Claims

Claims 1, 9-10, 13-15, and 19-31 are currently pending. Claims 1, 9, 10, 13-15, 19, 20, 21-26, 32, and 33 have been amended. Claims 2-4, 6-8, 12, and 16-18 have been cancelled without prejudice.

B. The Claims Are Patentable Over Supersaxo In View Of Bodmer Pursuant to 35 U.S.C. §103(a)

The Examiner rejected claims 1-31 under 35 U.S.C. § 102(e) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 5,470,582 to Supersaxo et al. (hereinafter "Supersaxo") in view of D. Bodmer et al., "Factors influencing the release of peptides and proteins from biodegradable parenteral depot systems (hereinafter "Bodmer"). Applicant respectfully disagrees that the claims are unpatentable over Supersaxo in view of Bodmer.

To establish a prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974); MPEP 2143.03.

Amended claim 1 states:

> preparing biodegradable porous microspheres comprising cationic functional groups from a mixture of a biocompatible material comprising cationic functional groups and a biodegradable polymer;
>
> adding a solution comprising a biopharmaceutical compound to the biodegradable porous microspheres;

incorporating the biopharmaceutical compound into the biodegradable porous microspheres through ionic interaction by suspending or equilibrating thebiodegradable porous microspheres in a solution comprising the biopharmaceutical compound at a pH beyond the pI of the biopharmaceutical compound; and

recovering and freeze-drying the biopharmaceutical-incorporated microspheres;

wherein the biopharmaceutical compound is over 5,000 dalton and is present in an amount of more than 10% by weight.

Amended Claim 21 states:

a biodegradable porous microsphere, comprising cationic functional groups from a mixture of a biocompatible material comprising cationic functional groups and a biodegradable polymer;

a biopharmaceutical compound, wherein the biopharmaceutical compound is positioned in the biodegradable porous microsphere; and

wherein the biopharmaceutical compound is over 5,000 dalton and is present in an amount of more than 10% by weight.

Support for amended claims 1 and 21 can at least be found in the Applicant's Specification. For example:

An embodiment may include processes, wherein said biodegradable porous microspheres having cationic functional groups are prepared from the blends of cationic surfactant or biocompatible materials having cationic functional group with biodegradable polymer. (Applicant's Specification, page 6, line 29-page 7, line 1);

a second step to incorporate a biopharmaceutical into the ionic porous microspheres by suspending the microspheres in an aqueous solution of biopharmaceutical. (Applicant's Specification, page 10, lines 10-12); and

An embodiment may include processes, wherein the composition is prepared by incorporation of an anionic biopharmaceutical into biodegradable porous microspheres having cationic functional groups and wherein the pH of incorporation solution is higher than the pI of the biopharmaceutical. (Applicant's Specification, page 6, lines 1-5)

The Examiner stated, "Supersaxo et al. discloses a controlled release pharmaceutical composition comprising a physiologically active agent dispersed in preformed porous polymeric microparticles. The active agent concentration may be up to about 10% by weight to achieve controlled release." (Office Action, page 3)

Claims 1 and 21 include a combination of features including, but not limited to, the feature of "wherein the biopharmaceutical is over 5,000 dalton and is present in an amount more than 10% by weight." Applicant submits that the cited art does not appear to teach or suggest at least the quoted features of claims 1 and 21.

Supersaxo appears to teach an "active agent concentration may be up to about 10% by weight to achieve controlled release." (Supersaxo, col. 5, l. 44-49) Supersaxo does not appear to teach or suggest biopharmaceutical present in an amount of more than 10%. Bodmer also does not appear to teach or biopharmaceuticals present in an amount of more than 10% by weight. Bodmer teaches "theoretical drug loading levels varying from 2 to 8%." (Bodmer, page 131) Applicant submits that the cited art does not appear to teach or suggest at least the quoted features of claims 1 and 21. Applicant respectfully requests removal of the rejections to claims 1 and 21 and the claims dependent thereon.

The Examiner also stated "[t]he microparticles are polymer of polylactic, polyglycolic, or copoly(lactice/glycolic) acid." (Office Action, page 3)

Claims 1 and 21 include a combination of features including, but not limited to, the features of "biodegradable porous microspheres comprising cationic functional groups." Applicant submits that the cited art does not appear to teach or suggest at least the quoted features of claims 1 and 21.

Supersaxo states "[t]he microparticles are prepared from any suitable polymeric material, such as polyesters, polyamides, polyanhydrides, and polyacrylates." (Supersaxo, column 5, lines 7-9) Supersaxo appears to teach microparticles that do not have a charge. The Examiner appears

to agree, stating "Supersaxo does not disclose the microparticles having accessible ionic functional groups." (Office Action, page 4)

Bodmer states:

> Osmotic effects, swelling of the device and ionic interactions e.g. such between polymer terminal carboxylic acid groups and basic polypeptides have to be taken into account for the release properties of these delivery systems, too. (Bodmer, page 136)

Bodmer does not appear to teach or suggest microspheres comprising cationic functional groups. Bodmer appears to teach forming microspheres in situ by interacting biopharmaceuticals with polymers. In addition, the interaction of a carboxylic acid group with a basic peptide creates an anionic-polymer and a cationic biopharmaceutical. Applicant submits that claims 1 and 21 use a cationic substrate with an anionic biopharmaceutical. Furthermore, Bodmer appears to teach using neutral compounds that have basic groups. Only mixing the compounds together generates ionic interactions. Applicant submits that in claims 1 and 21 the cationic and the anionic groups are present before mixing the biopharmaceutical and the biodegradable porous microspheres.

Applicant submits that the cited art does not appear to teach or suggest at least the quoted features of claims 1 and 21. Applicant respectfully requests removal of the rejection to claims 1 and 21 and the claims dependent thereon.

The Examiner also rejected claim 1 stating, "[m]icrospheres were produced by a modified triple-emulsion technique." (Office Action, page 4)

Claim 1 includes a combination of features including, but not limited to, the features of "incorporating a biopharmaceutical into the microspheres through ionic interaction by suspending or equilibrating the microspheres in a solution comprising the biopharmaceutical at a pH beyond pI of biopharmaceutical" and "recovering and freeze-drying the biopharmaceutical-incorporated microspheres." Applicant's Specification states:

> Therefore, there are two main advantages for preparing sustained release biopharmaceutical compositions. One is a protection of the denaturation and irreversible aggregation of the biopharmaceutical during incorporation process because the incorporation is achieved under absence of an organic solvent that is very harmful to a biopharmaceutical especially under co existence of aqueous solution. (Applicant's Specification, page 4, lines 18-22)

Applicant's Specification also states:

> Due to the hydrophilic nature of most protein drugs, water in oil in water (w/o/w) double emulsion solvent evaporation technique is frequently used for encapsulating protein into a biodegradable polymeric matrix. In this process, an aqueous protein solution is emulsified into a polymer solvent phase and this primary emulsion is further dispersed into a large volume of water phase containing an appropriate surfactant. Inevitably, protein drugs are exposed to a water/organic solvent interface. Most protein drugs are denatured and non covalently aggregated during this primary emulsion stage. Resultantly, the final product of protein loaded microspheres typically showed an initial burst release of relatively native protein portions which were loosely bound to polymeric microspheres followed by no significant release of irreversibly aggregated protein portions for miy prolonged time (page 2, lines 16-27.)

Supersaxo states, "20 mg of labeled active agent-containing microsphers were dissolved in 2 mL of methylene chloride and 20 mL of scintillation cocktail...and the active agent concentration." (Supersaxo, column 7, lines 9-13) Supersaxo appears to teach exposing biopharmaceuticals to a water/organic interface. Supersaxo does not appear to teach at least the quoted features of the claim.

Brodmer states:

> Microspheres were produced by a modified triple-emulsion technique [7]. Octreotide was dissolved in a small amount of water...and the solution was intensively homogenized using an Ultra-Turrex T25...into a solution (40%) of DL-PLG-GLU in methylene chloride. (Bodmer, page 130)

Brodmer appears to teach exposing biopharmaceuticals to a methylene chloride/water interface. Brodmer does not appear to teach or suggest inhibiting protein denaturation. Applicant submits that the cited art does not appear to teach or suggest at least the quoted

features of claim 1 and the claims dependent thereon. Applicant respectfully requests removal of the rejection to the claims.

C. Additional Comments

Applicant submits that all claims are in condition for allowance. Favorable reconsideration is respectfully requested.

Applicant hereby requests a one-month extension of time. A fee authorization for a one-month extension of time is included. If any additional extension of time is required, Applicant hereby requests the appropriate extension of time. If any additional fees are required or if any fees have been overpaid, please appropriately charge or credit those fees to Meyertons, Hood, Kivlin, Kowert & Goetzel, P.C. Deposit Account Number 50-1505/5333-02600/EBM.

Respectfully submitted,

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